HED DOC. NO. 013895

December 15, 1999

MEMORANDUM

SUBJECT: ***VINCLOZOLIN*** - Reassessment Report of the FQPA Safety Factor Committee.

NOTE: THIS REPORT REPLACES THE PREVIOUS REPORT OF THE FQPA SAFETY FACTOR COMMITTEE DATED MARCH 30, 1999 (HED Doc. No. 013288).

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THROUGH: Ed Zager, Chairman
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PC Code: 113201

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on November 22, 1999 to re-evaluate the hazard and exposure data for Vinclozolin and maintained that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) should be retained at 10x when assessing the risks posed by the use of this pesticide. This report replaces the previous report of the FQPA Safety Factor Committee dated March 30, 1999 (HED Doc. No. 013288).

I. HAZARD ASSESSMENT

(*DRAFT Memorandum:* D. Anderson and E. Mendez to W. Hazel dated November 17, 1999)

On September 16, 1999, the HED Hazard Identification Assessment Review Committee (HIARC) reviewed additional data provided on ventral prostate weight from perinatal studies with vinclozolin. On November 4, 1999, the HIARC evaluated the literature data on potential effects on the brain and other potential neurotoxic effects from perinatal testing of substances, including vinclozolin, that have androgenic and antiandrogenic effects on exposed offspring.

1. Comprehensive Evaluation of the Open Literature

The HIARC considered an evaluation of the currently available literature related to androgenic activity with compounds like vinclozolin (a total of 89 published articles - including reviews and research articles). The published literature indicates that there is sufficient evidence that compounds like vinclozolin that may disrupt the neuroendocrine system through their anti-androgenic properties can cause significant changes in the morphological and biochemical development of the nervous system. The effects of these changes can be monitored at the molecular level by use of immunocytochemistry, fluorescent *in situ* hybridization (FISH), mobility shift assays, or transcription assay techniques. And at the organism level, behavioral tests can be conducted to ascertain the effects of anti-androgen treatment on learning and behavior (*Memorandum:*E. Mendez to J. Rowland and P. Wagner dated October 27, 1999).

2. Adequacy of the Toxicology Database

The HIARC concluded that a **developmental neurotoxicity study (DNT) in rats with an expanded protocol is required** due to concern for the anti-androgenic properties of vinclozolin and its metabolites. Since the current DNT study protocol may not be sufficient to detect the subtle findings reported in the open literature and to assess the relevant endpoints for vinclozolin, an expanded protocol is required.

3. Determination of Susceptibility

Prenatal studies in rats demonstrate enhanced susceptibility of rat fetuses as compared to maternal animals following *in utero* exposure to vinclozolin. In the developmental toxicity study in rats, anti-androgen related effects, such as reduced anogenital distance (AGD), areola/nipple development, and ventral prostate weight decrease, occur at lower dose levels than effects on mothers dosed at the same dose levels and time period. There was no indication of increased susceptibility to young rabbits following *in utero* exposures or in the prenatal dermal developmental toxicity studies in rats. Additionally, in the 2-generation reproduction study in rats, effects in the offspring were observed only at or above dose levels causing parental toxicity.

II. EXPOSURE ASSESSMENT

1. Dietary Exposure Considerations
(*Correspondence:* W. Hazel to B. Tarplee dated November 18, 1999)

Tolerances are established for the combined residues of the fungicide vinclozolin and its metabolites containing the 3,5-dichloroaniline moiety in or on several raw agricultural commodities at levels ranging from 1 to 25 ppm (40 CFR§180.380). Tolerances are currently undergoing tolerance reassessment for the HED Chapter of the RED. High consumption food items for infants and children include strawberries and stone fruit, however these tolerances will no longer be supported after January 2000. New uses are currently proposed for canola and snap beans. Codex MRLs are established for many commodities and are similar or identical to U.S. tolerances.

Although monitoring data are available for vinclozolin, these data are not considered to be useful for risk assessment since only parent vinclozolin was analyzed. Field trial data on vinclozolin and its metabolites containing the 3,5-dichloroaniline moiety are available on all crops. Virtually all of the field trial samples bore detectable residues ranging from 0.05-8.4 ppm. In addition to residue data, percent crop treated (%CT) and percent crop imported (%CI) data have been provided by the Biological and Economic Analysis Division (BEAD).

The HED Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from acute and chronic dietary exposure to vinclozolin residues in food. These analyses will be performed using reassessed tolerance level residues and refined using the entire distributions of field trial data along with % CT and %CI data resulting in a less exaggerated representation of dietary food exposure resulting from the use of vinclozolin.

2. Drinking Water Exposure Considerations
(*Correspondence:* W. Hazel to B. Tarplee dated November 18, 1999)

The environmental fate data base for vinclozolin is adequate for the characterization of drinking water exposure. The data indicate that parent vinclozolin and degradates are potentially mobile and can be persistent depending upon the environmental conditions. Therefore, EFED concluded that vinclozolin has the potential to contaminate surface and ground water. Additionally, residues originating from parent vinclozolin may accumulate from year to year and be available for rotational crop uptake.

No groundwater studies are available for vinclozolin. Groundwater EECs were estimated using the SCI-GROW model. This estimate represents both acute and chronic exposure and were recommended for use in the risk assessment.

No available surface water monitoring data are available for vinclozolin. Surface water EECs were estimated using GENEEC (version 1.2). Peak and 56-day mean exposure estimates were generated using the maximum application rates for strawberries, peaches, and turf. Estimates of drinking water concentrations of vinclozolin derived from surface water are **currently being refined** using PRZM/EXAMS. These estimates will include the proposed uses and the new application rates.

3. Residential Exposure Considerations
(*Correspondence:* J. Dawson to B. Tarplee dated November 18, 1999)

Although there are no registered residential uses for vinclozolin (direct application in residential areas is not allowed by current labeling), there is concern for non-occupational post-application exposure to infants and toddlers resulting from treated sod placed around the home or other recreational areas. Golf course greens and tees can also be treated which could result in exposure to the general public (low exposures for this scenario are anticipated).

The *Standard Operating Procedures For Residential Exposure Assessment* will be used as the basis for the risk assessment for vinclozolin. There are a number of dislodgeable foliar residue studies for vinclozolin including a turf study. Additionally, there is a Jazzercize exposure study on turf. These data will be used, where appropriate, to calculate residue concentrations and exposures over time instead of using the Agency default assumptions. These chemical-specific data were generated using maximum application rates which result in conservative exposure estimates.

III. RISK CHARACTERIZATION

1. FQPA Safety Factor Recommendation

The FQPA SFC recommended that the safety factor for protection of infants and children (as required by FQPA) should be **retained at 10x for Females 13-50 and Infants and Children subpopulations when assessing acute dietary (where applicable) and short-/intermediate-term residential (non-occupational) exposures.** The Committee also recommended that when assessing **chronic dietary exposures, the safety factor should be retained at 10x for All Population Subgroups.**

2. Rationale for Requiring the FQPA Safety Factor

The FQPA SFC concluded that a safety factor is required because:

< there is evidence of increased susceptibility following *in utero* exposure to vinclozolin in the prenatal developmental toxicity study in rats; and

< a developmental neurotoxicity study in rats with an expanded protocol is required for vinclozolin due to concern for the anti-androgenic properties of vinclozolin and its metabolites.

3. Application of the Safety Factor - Population Subgroups / Risk Assessment Scenarios

When assessing **Acute Dietary (if applicable)* and Short-/Intermediate-term Residential (Non-occupational) Exposures,** the safety factor should be **Retained at 10x** for the **Females 13-50** and for the **Infants and Children Subgroups** since an increase in susceptibility was observed following *in utero* exposure to rats in the developmental study (which could potentially occur after a single dose); and since there is a data gap for the developmental neurotoxicity study which could provide information relevant to all population subgroups and exposure durations.

*Since no appropriate dose/endpoint was identified by the HIARC for use in acute dietary risk assessments for Infants and Children, the safety factor is not applicable to this population subgroup at this time.

When assessing **Chronic Dietary Exposure,** the safety factor should be **Retained at 10x** for **All Population Subgroups** since there is concern for reproductive effects (seen in teste, sperm, epididymides, and ovaries) observed at one or mores doses in the chronic studies used to establish the chronic RfD. Additionally, there is a data gap for the developmental neurotoxicity study which could provide information relevant to all population subgroups and exposure durations.